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Extended Abstract
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Euro Pathology 2018: The Development of Autoimmune Membrano-Proliferative Glomerulonephritis (Type II) In a Female Patient with Serological Combined Autoantibodies against Complement 3b and Factor B: Case Report - Wu KY2 - Institut für Pathologie, Charité Campus Mitte, Universitätsmedizin Berlin, Germany.

Wu KY2

Institut für Pathologie, Charité Campus Mitte, Universitätsmedizin Berlin, Germany.

Case presentation: A 3-year-old girl developed hematuria (HU), proteinuria (PU) and hypo complementemia (HC) with no identified cause; the first renal biopsy indicated MPGN which resembled MPGN type I. After treatment with methylprednisolone and cyclophosphamide (CT), nephritic syndrome (HU plus PU) withdrew but often relapsed. At the age of 7, the clinical condition suddenly worsened, the UP and urinary sediment activity increased and the rate of glomerular filtration rapidly decreased; simultaneously, autoantibodies against complement 3b (C3b) and factor B remained detected with high titers. The second renal biopsy presented a typical glomerular lesion of type II MPGN with diffuse cell crescents; the patient was treated with methylprednisolone plus plasmapheresis and rituximab, but renal failure continued. She started peritoneal dialysis at the age of 9 and received a kidney transplant at the age of 11; after the transplant, she received routine immunosuppression plus plasmapheresis and rituximab (anti-CD20 globulin), and experienced clinical remission, except for persistent HC. Nephritic syndrome relapsed at the age of 13 and the third renal biopsy confirmed a relapse of type II MPGN; subsequently, Eculizumab (anti-C5 monoclonal antibody) was administered, which significantly improved clinical status.

Introduction

Membrano-proliferative glomerulonephritis (MPGN), a rare form of chronic nephritis, is mainly diagnosed by renal biopsy at the level of light microscopy (LM) on two pathological profiles of glomerular lesion: (a) mesangial and endothelial hyper cellularity; and (b) thickening of the glomerular capillary walls due to the mesangial interposition and the double contours of the glomerular basement membrane (GBM). MPGN can be idiopathic or secondary in etiology; most idiopathic and secondary MPGNs present similar pathological appearances. Idiopathic MPGN can be divided into types I, II and III based on ultrastructural details since the LM characteristics are mostly indistinguishable between 3 types. Regardless of the types, most MPGNs arise from abnormalities in the alternative complement pathways due to systemic activation of C3 and deposition of C3 cleavage products along the GBM. Excessive activation of C3 convertase can induce permanent activation which completes and improves the alternative cascade of complement. C3b and factor B, two individual components of C3 convertase, can enhance the activity of C3 convertase after C3b and factor B are motivated by acquired genetic or pathogenetic mechanisms. In 2011, Chen et al reported two patients who had the combined serological autoantibodies to C3b and factor B; the younger patient was detected with a heterozygous deficiency of genes coding for proteins 1 linked to complement factor H (CFHR1) and 3 (CFHR3); she clinically manifested persistent hypo complementarian (HC) and nephritic syndrome (hematuria HU plus proteinuria PU), eventually entered the uremia and underwent an allograft transplant. During the development of type II MPGN, she underwent three renal biopsies when the clinical situation changed: (i) the first episode of nephrotic syndrome; (ii) rapid progression of renal failure; and (iii) relapse of post-transplant nephritic syndrome. Type II MPGN is a rare form of MPGN and clearly has a poorer prognostic significance compared to types I and III. We examined these biopsies and analyzed the clinical and pathological characteristics associated with the development of autoimmune MPGN type II.

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Clinical and Laboratory Evidences and Pathological Features

The 3-year-old girl noticed that her urine was a dark red color in the absence of any clinical cause, namely, an infection of the respiratory / urinary tract, blood spots on the skin or taking medication, and the laboratory examination showed HU 3+ and PU 3+, a low serum concentration of C3, C4 and the serum creatinine concentration (Scr) were at normal values. In addition, anti-nuclear antibodies and antibodies against double-stranded DNA were negative. Renal biopsy at this time diffuse end capillary hyper cellularity, intracapillary neutrophil infiltration, interposition of mesangial cells, and focal segmental capillary disturbance with cell crescents (involving 3 of 36 glomeruli). Immunofluorescence (IF) microscopy showed focal sub endothelial and mesangial granular deposits which stained 3+ for C3 and 1+ for C1q. Electron microscopy (EM) found focal sub endothelial and mesangial granular deposits (EDD), intramembranous mesangial interpositions, but the intramembranous or sub epithelial areas were free of EDD. The LM aspect resembled post-streptococcal glomerulonephritis, but the ultrastructural results suggested the onset of MPGN. Clinical improvement could be observed with methylprednisolone plus cyclophosphamide therapy, while HU and PU often relapsed, accompanying a persistent and often deep depression of C3 (the lowest level of C3c was 33 mg / dL) during the following 4 years.

At the age of 7, the clinical situation worsened significantly with the active urinary sediment, heavy PU (maximum at 3.17 g / L), rapidly increasing the serum creatinine concentration and the glomerular filtration rate (GFR) decreased. In addition, the combined autoantibodies of complement 3b (C3b) and factor B were detected with high titers in circulation, leading to an extremely low C3 level. The second renal biopsy presented prominent mesangial hyper cellularity, dense linear transformation of the peripheral double GBM and the interposition of mesangial cells, and diffuses a linear sub endothelial and intramembranous peripheral staining of 3+ for C3, 1+ for C1q. The ME showed the typical appearance of type II MPGN with an EDD in the form of an intramembranous linear band and a granular mesangial EDD. In addition, segmental capillary rupture and extra capillary proliferation were observed in 50% of the glomeruli, which presented convincing evidence to explain acute renal failure. The girl was treated with 2 pulses of methylprednisolone, 3 infusions of fresh plasma and 15 plasmaphereses. In addition, rituximab (anti-CD20 globulin) was also administered at a dose of 375 mg / m2. At the same time, secondary complications of renal failure, including hypertension, anemia and hyperkalemia, were well controlled. However, deep kidney failure has progressed; she started peritoneal dialysis at the age of 9.

Conclusion: The pathological aspect of type II MPGN can be variable but not totally irrelevant depending on the clinical conditions at the time of the biopsy.

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